Technoeconomic evaluation of separation solvents and technologies for Continuous Pharmaceutical Manufacturing (CPM) of Four Key Drug Substances (DS)

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KEYWORDS: Continuous Pharmaceutical Manufacturing (CPM), Technoeconomic Optimisation, Active Pharmaceutical Ingredients (APIs), Separations, Process Design.

ABSTRACT

Continuous Pharmaceutical Manufacturing (CPM) has the potential to revolutionise the pharmaceutical industry via operating and economic benefits over traditional batch techniques. Establishing efficient continuous separation processes following continuous flow syntheses of active pharmaceutical ingredients (APIs) is essential to obtain the desired physical form of drug substance (DS) and successful CPM implementation. Process modelling and optimisation are essential tools for rapid screening of design alternatives to establish cost optimal process configurations for separation unit operations in integrated upstream CPM plants. This paper presents the technoeconomic optimisation for total cost minimisation for the continuous liquid-liquid extraction (LLE) of (S)-warfarin and the continuous mixed suspension mixed product removal (MSMPR) crystallisation of cyclosporine, paracetamol and aliskiren. Optimisation of continuous LLE of (S)-warfarin compares candidate separation solvents and operating temperatures with solvent feed rate and LLE tank residence time as decision variables; optimisation of continuous crystallisation processes compares the number of implemented crystallisers with MSMPR operating temperatures and residence times as decision variables. Capital (CapEx), operating (OpEx) and total expenditures are compared for different designs, elucidating cost-optimal configurations for each API with their attained recoveries and respective operating conditions. This work demonstrates the value of total cost minimisation via nonlinear optimisation prior to expensive experimental investigations and the potential of the economic benefits attainable via CPM for these APIs.

INTRODUCTION

Continuous Pharmaceutical Manufacturing (CPM) has been widely recognised for its potential for significant operating and economic benefits to manufacturing firms over traditionally implemented batch methods (1, 3). Numerous demonstrations of active pharmaceutical ingredient (API) continuous flow syntheses and a focus on process modelling (4) indicate a keen interest of judicious industrial transition from batch to CPM methods. While several end-to-end CPM campaigns (5, 7) are documented, numerous challenges remain in integrated continuous separations, (8) presenting a bottleneck to realising the benefits of fully continuous manufacturing in the pharmaceutical industry. Significant research efforts in continuous separation technologies are addressing this issue.

Continuous purifications and separations following continuous API synthesis are essential in obtaining drug substances (DS) in their desired final form in integrated CPM campaigns. Liquid-liquid extraction (LLE) is often employed to purify reactor effluent streams prior to subsequent operations, and can be implemented in continuous mode for pharmaceutical manufacturing (9, 10).

Crystallisation is also an important separation method for pharmaceutical manufacturing due to the dominance of solid drug products sold by the industry; continuous crystallisation methods can offer greater process flexibility and product quality over batch crystallisations (11), which have issues with batch-to-batch variability. Membrane-assisted crystallisation methods (12) and simulated moving bed (SMB) chromatography (13) have also been integrated into CPM campaigns to attain target API purities in final product streams.

Screening of promising candidate process configurations is important in the development of CPM routes (14, 15) Ultimately, any candidate process must be technologically feasible and economically viable. Process modelling, simulation and technoeconomic optimisation of CPM processes can be utilised to establish cost-effective process configurations (16, 19). Nonlinear optimisation of upstream CPM plants with integrated conceptual continuous LLE and/or crystallisation stages can elucidate optimal operating parameters corresponding to minimum total costs.

Process modelling and optimisation case studies of candidate APIs is useful in highlighting CPM benefits for experimentally demonstrated CPM routes. This paper describes the total cost minimisation via nonlinear optimisation of upstream CPM plants for four APIs: (S)-warfarin, an anticoagulant, cyclosporine, an immunosuppressant, paracetamol, the popular analgesic, and aliskiren, an antihypertensive. First, experimental demonstrations of the continuous processes for these APIs from the literature and the modelling and optimisation methodologies implemented are described. We then present a comparative analysis of minimum total costs for different separation process configurations, elucidating optimal configurations for each API. A critical discussion of the methodologies and results and the utility of process modelling and optimisation for screening candidate CPM processes is then provided as an outlook on this vibrant research field.

PROCESS MODELLING AND OPTIMISATION

(S)-warfarin: continuous flow synthesis and Liquid-Liquid Extraction (LLE)

The process model for the CPM of (S)-warfarin considers both continuous flow synthesis and conceptual continuous separation stages. The continuous flow synthesis of (S)-warfarin features a single-step synthesis followed by a LLE

stage (Figure 1). Nucleophilic addition of 4-hydroxycoumarin to benzalacetone with trifluoroacetic acid (TFA) and a chiral amine catalyst at 75 °C in 1,4-dioxane occurs in a plug flow reactor (PFR), with a reported conversion of 61% (20). Aqueous HCl (10% w/w) is added to the reactor effluent prior to LLE (20). Here, we comparatively evaluate candidate separation solvents for a conceptual single-stage continuous LLE process. Candidate solvents must allow rapid phase splitting upon LLE solvent addition to the PFR effluent and be considered acceptable with respect to EHS criteria. We consider ethyl acetate (EtOAc), isopropyl acetate (iPrOAc), isobutyl acetate (iBuOAc), 1-heptanol (HepOH), 1-octanol (OcOH) and n-heptane (nHep) as candidate LLE solvents.

The model for continuous LLE is the same as described in our recent technoeconomic optimisation study (16). Continuous LLE processes are modelled as single-stage mixer-settlers. In the continuous LLE unit, API transfers into the dispersed (organic) product phase from the process mixture. Detailed mass transfer correlations are used for accurate description of API recovery into the product phase (21). Attainable API recoveries from LLE depend upon the operating temperature (T_{LLE}), the LLE tank residence time (τ_{LLE}) and the LLE solvent-to-feed ratio by mass (r). We consider LLE operating temperatures of 20, 40 and 60 °C for varying tank residence times and solvent feed rates. Theoretical phase compositions and mixture API solubilities are predicted via extensive UNIFAC modelling. Stage efficiencies as a function of τ_{LLE} allow calculation of API concentrations in the product phase.

Cyclosporine, paracetamol and aliskiren: continuous cooling crystallisation

The process models for CPM of cyclosporine, paracetamol and aliskiren consider continuous crystallisation using mixed suspension mixed product removal (MSMPR) crystalliser cascades. MSMPR crystallisers are continuous stirred tank designs easily adapted from existing batch vessels and do not suffer from rapid fouling problems associated with tubular designs. MSMPR cascades have been experimentally demonstrated for cyclosporine, (22) paracetamol (23) and aliskiren (Figure 1)(24). A clear mother liquor feed stream containing dissolved API enters the first crystalliser, with the product mother liquor entering the subsequent crystalliser; product magma is withdrawn from the final crystalliser in series.

The MSMPR process model describes crystal population balances, crystallisation kinetics and mass balance equations (22-24). The solution of the process model for a desired plant capacity is described in our previous work (25). Process performance is a function of the number of crystallisers in the cascade (N), residence times (τi) and operating temperatures (Ti) of each crystalliser. We explicitly consider cascades of N = 1, 2 and 3 crystallisers for varying crystalliser residence times and temperatures.

Nonlinear optimisation problem formulation

The objective of the nonlinear optimisation problem is total cost minimisation. Total costs are calculated as the sum of capital (CapEx) and operating (OpEx) expenditures over the plant lifetime (t), discounted by the interest rate (y).

$$\min Cost = CapEx + \sum_{i=1}^{t} \frac{OpEx}{(1+y)^i} \quad (1)$$

Constraints on the total cost objective function for the continuous LLE of (S)-warfarin are

$$0 < T_{LLE} \quad (2)$$

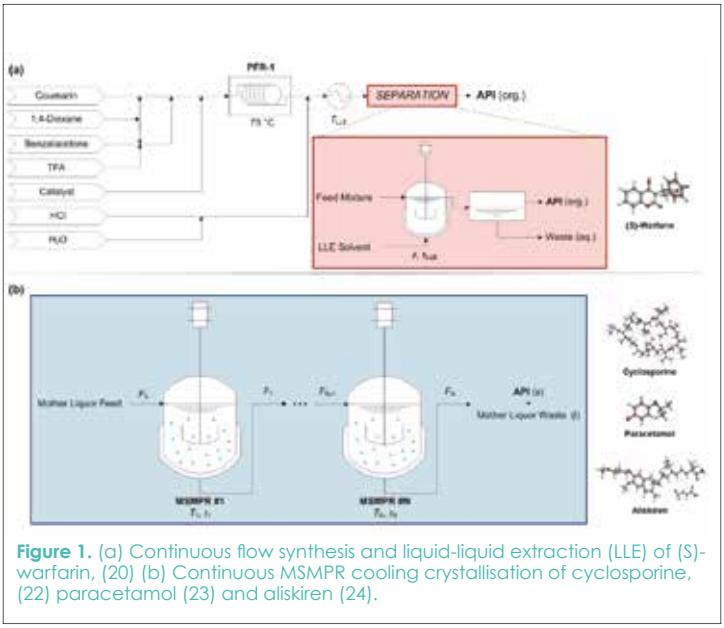

Figure 1. (a) Continuous flow synthesis and liquid-liquid extraction (LLE) of (S)-warfarin, (20) (b) Continuous MSMPR cooling crystallisation of cyclosporine, (22) paracetamol (23) and aliskiren (24).

$$1 < r < 4 \quad (3)$$

and constraints for continuous MSMPR crystallisation of cyclosporine, paracetamol and aliskiren are

$$-10\ °C \le T_1 \le \ldots \le T_N \le 20\ °C \quad (4)$$

$$T_1 = \ldots = T_N \quad (5)$$

$$\sum_{i=1}^{N} \tau_i \le 15\ h \quad (6)$$

CapEx is the sum of battery limits installed costs, working capital and construction; OpEx is the sum of materials, utilities and waste handling costs (3). Annual operation of 8,000 hours per year is considered. All equipment capacities and material requirements are scaled to account for process (reaction and separation) inefficiencies to meet a plant capacity of 100 kg per annum. All assumptions associated with the nonlinear objective function formulation are summarised in Table 1.

Parameter	Value	Units
Plant API Capacity	100	kg API per annum
Annual Operation	8,000	hours per annum
Plant lifetime, *t*	20	years
Interest rate, *y*	5	%

Table 1. Economic analysis parameters for total cost objective function formulation.

COMPARATIVE TECHNOECONOMIC ANALYSIS

(S)-warfarin

Figure 2a shows attained API recoveries and the corresponding optimal operating parameters for each LLE solvent for CPM of (S)-warfarin. Generally, the higher the API solubility in the (pure) LLE solvent, the higher the attainable recovery, as expected. There are some exceptions to this trend due to the interconnected dependence of recovery on tank residence time and API solubility in the product (organic) phase, which is a function of temperature (T_{LLE}), and product phase composition. Optimum LLE tank residence times (τ_{LLE}) also vary across different LLE solvent choices due to its affect on LLE stage efficiency (21). In all cases, the LLE solvent feed rate (r) is pushed to the lower bound (r = 1) as defined in the nonlinear objective function constraints (eqs. 2 and 3). The amount of fresh LLE solvent used directly affects OpEx components (materials, utilities and waste handling) and thus

varies strongly affect total costs. Increased solvent feed rates do not attain sufficient increases in recovery to merit total cost reductions. Optimum operating temperature varies between different solvent choices due to its effect on product phase compositions, physical properties, their API solubilities and mass transfer phenomena (21).

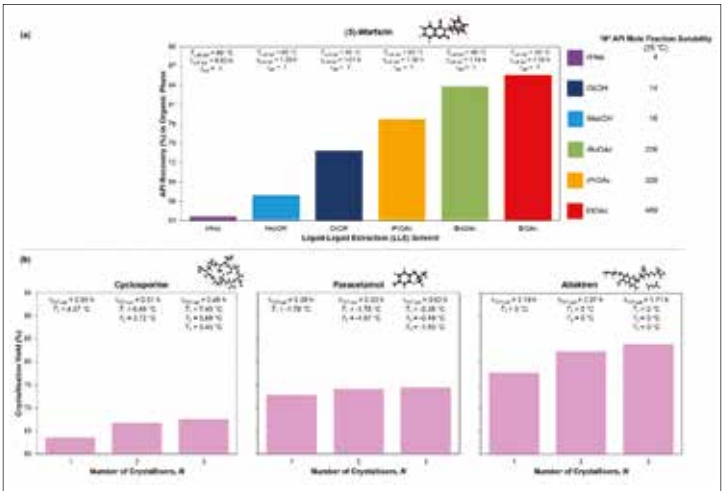

Figure 2. Attainable process performances and cost optimal process configurations for (a) continuous LLE of (S)-warfarin, (b) continuous crystallisation of cyclosporine, paracetamol and aliskiren.

Minimum total cost components (CapEx and OpEx) of different LLE configurations for CPM of (S)-warfarin are shown in Figure 3a. The best performing LLE solvent is iBuOAc, attaining the lowest total costs (293.87·106 GBP); the following best performing solvents are EtOAc (299.91·106 GBP) and iPrOAc (299.93·106 GBP). Comparable performances of these solvents are observed due to their similar molecular structures (low MW esters) and polarities, hence inducing similar LLE phase compositions upon phase splitting and thus attaining comparable API recoveries. For the same reason, HepOH (339.43·106 GBP) and OcOH (324.54·106 GBP) also perform comparably. The poorest performance (highest minimum total costs) is attained by nHep usage (350.52·106 GBP).

Cyclosporine, paracetamol and aliskiren

Minimum total cost components for different MSMPR configurations for cyclosporine, paracetamol and aliskiren are shown in Figure 2b; crystallisation yields and optimal operating configurations and parameters are shown in Figure 3b. For each API, minimum total costs are attained by implementing one crystalliser for the specified plant capacity (100 kg API per annum). Consideration of higher capacities may affect this result and should be investigated explicitly as part of a wider, life cycle assessment (LCA) study. Increasing the number of implemented crystallisers increases CapEx, despite decreasing total crystallisation residence times; this is due to the additional pumps and cooling equipment required. Increasing the number of implemented crystallisers leads to increased yields and higher operating temperatures (i.e. less cooling required). Rigorous flow and temperature control is required to maintain crystalliser operation at optimal conditions (residence times and temperatures); implementation of process analytical technology (PAT) is essential for successful CPM implementation.

CONCLUSIONS

The development of continuous separation technologies for integration into end-to-end campaigns is essential for successful implementation of CPM processes (26).

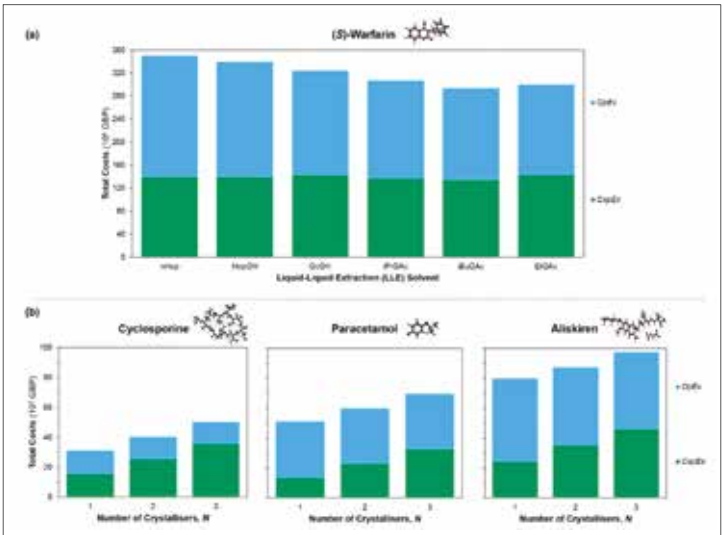

Figure 3. Minimum total cost components for different process configurations for (a) (S)-warfarin and (b) cyclosporine, paracetamol and aliskiren.

This paper presents the implementation of conceptual process modelling and optimisation of continuous LLE for (S)-warfarin and MSMPR crystallisation for cyclosporine, paracetamol and aliskiren, considering suitable constraints on tank residence times and LLE solvent feed rates for (S)-warfarin, and on crystalliser residence times and operating temperatures for cyclosporine, paracetamol and aliskiren. Nonlinear optimisation results show that isobutyl acetate (iBuOAc) operating at 60 °C is the best LLE solvent for CPM of (S)-warfarin fed at a solvent-to-feed rate (r, mass basis) of 1. For the crystallisation of cyclosporine, paracetamol and aliskiren, implementation of one crystalliser and low operating temperatures attains the lowest total costs for the plant capacity considered (100 kg per annum). Plant designs and technoeconomic evaluation results presented here merit further corroboration via tailored experimental campaigns under the prescribed parameters (or even wider intervals thereof). This study illustrates the value of modelling and optimisation studies for process configuration screening, before costly experimental investigations are undertaken for the development of continuous plants and their implementation in industrial practice.

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